

Effect of brachial-ankle pulse wave velocity combined with blood pressure on cardio-cerebrovascular events

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Abstract. The aim of the present study was to evaluate the effect of brachial-ankle pulse wave velocity (baPWV) combined with blood pressure (BP) on cardio-cerebrovascular events. Participants who received health examinations during the periods 2010-2011, 2012-2013 and 2014-2015 were recruited. The participants were divided into four groups according to their BP and baPWV levels as follows: Normotension + low baPWV, normotension + high baPWV, hypertension + low baPWV, and hypertension + high baPWV. The cumulative incidence of cardio-cerebrovascular events was calculated using life-table analysis, and the associations of BP and baPWV with cardio-cerebrovascular events were analyzed using a multivariate Cox proportional hazards regression model. Receiver operating characteristic curves were used to calculate the predictive values of baPWV combined with BP, baPWV alone or BP alone for cardio-cerebrovascular events by comparing their area under the curve (AUC) using the normal approximation method. There were 20,310 participants with a mean age of 50.13±0.09 years in the present study, including 13,240 males. A total of 278 participants developed a cardio-cerebrovascular event after a mean follow-up period

of 3.34±1.82 years. The cumulative incidence of cardio-cerebrovascular events in the normotension + low baPWV, normotension + high baPWV, hypertension + low baPWV and hypertension + high baPWV groups was 0.2, 0.9, 0.8 and 3.1%. Multivariate Cox proportional hazards regression analysis showed that compared with the normotension + low baPWV group, the risks of cardio-cerebrovascular events in the normotension + high baPWV, hypertension + low baPWV and hypertension + high baPWV groups were increased after adjusting for confounding factors, and their hazard ratios (95% CI) were 4.18 (2.23-7.83), 3.00 (1.39-6.47) and 9.34 (5.14-16.96), respectively. The AUC values for the predictive values of baPWV combined with BP, baPWV alone and BP alone on cardio-cerebrovascular events were calculated to be 0.744, 0.677 and 0.698, respectively. In conclusion, high baPWV accompanied by hypertension could increase the risk of cardio-cerebrovascular events. The predictive value of baPWV combined with BP on cardio-cerebrovascular events is superior compared with that of either baPWV or BP alone.

Introduction

Hypertension is a risk factor for cardio-cerebrovascular events, which leads to a series of severe complications, including myocardial infarction (MI), heart failure, stroke and chronic kidney disease (1-4). Atherosclerosis is not only regarded as a sign of vascular aging, but also a risk factor for potential cardio-cerebrovascular events (5,6). Previous research showed that the risk of cardiovascular death exceeds 50% in hypertensive patients compared with non-hypertensive individuals, even if the blood pressure (BP) of patients is reduced to 140/90 mmHg after therapy (7,8). In addition, atherosclerosis serves an important role in the prognosis of cardio-cerebrovascular events (7). Niiranen *et al* (7) found that arteriosclerosis accompanied with hypertension is a risk factor for cardio-cerebrovascular mortality after a 12.6-year follow-up study of 2,127 cases in the general population. Song *et al* (9) observed a higher incidence of stroke in patients with arteriosclerosis and hypertension in a 4.5-year follow-up

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study of 3,310 hypertensive patients, especially those with higher BP. Therefore, from these previous observations it could be speculated that the assessment of arteriosclerosis combined with BP maybe an improved predictor for cardio-cerebrovascular events. However, these previous studies on the correlation between cardio-cerebrovascular events and arteriosclerosis combined with BP have certain shortcomings, namely the limited number of cases and specific populations.

The carotid-femoral pulse wave velocity (cfPWV) is considered the gold standard for assessing arteriosclerosis, but its measurement is relatively complex (10,11). The use of cfPWV is often limited in research due to the inconvenience associated with the measuring devices and processes used. The pulse volume waveforms were recorded through a semiconductor pressure sensor, with the sample acquisition frequency for PWV set at 1,200 Hz (12). There is a good correlation between brachial-ankle pulse wave velocity (baPWV) and cfPWV (13). The baPWV is a simple and reproducible measurement that has the potential to be a sensitive tool for evaluating arteriosclerosis. Indeed, a previous study has shown that the correlation between baPWV and cardiovascular risk factors is stronger compared with that of cfPWV (9). Therefore, the aim of the present study was to evaluate the effect of baPWV combined with BP on cardio-cerebrovascular events. The Kailuan study (registration number: ChiCTR-TNC-11001489) is a study assessing the risk factors of cardiovascular diseases based on functional community populations, which consists of five elements: Population, region, system, policy and institution. In order to clarify the prevalence of chronic diseases among the occupational population in China, since June 2006, health check-ups were conducted and data was collected concerning the endpoint events, every 2 years, for employees and retirees of the Kailuan Group. From January 2006 to June 2007, 101510 on-the-job and retired workers took part in health examination, 81,110 were males and 204,00 were females. Thus far, this study has measured and collected baPWV data from parts of the population between 2010 and 2015. Based on data collected from the Kailuan study, the association between baPWV combined with BP and cardio-cerebrovascular events plus possible risk factors was analyzed in the present study.

At present, primary hypertension accounts for the vast majority of cases of hypertension in China (95%), and is often considered to be the leading risk factor for cardiovascular mortality (14-16). Previous studies have stated that ~200 million people in China have hypertension, but few receive treatment or achieve appropriate control of their BP (17-25). Since, primary hypertension is so common, and is highly prevalent in the Kailuan study cohort, primary hypertension was the focus of the present study and patients with secondary hypertension, including aldosteronism, pheochromocytoma and renin-secreting tumor, were excluded.

The prevalence of diabetes mellitus (DM) in China has increased significantly over recent decades, and national representative surveys reveal a rise from ~0.9% in adults aged >30 years in 1980 to 11.6% in adults aged >18 years in 2010 (26,27). Previous studies have reported that the overall combined prevalence of diagnosed and undiagnosed diabetes in China increased from ~2.5 to ~10.9% between 1994 and 2013 (28,29). Another study suggested that China has overtaken India and has become the global epicenter of a diabetes

epidemic, with ~92.4 million adults affected (30). As a result of rapid economic development, urbanization and aging, China is facing a high and increasing burden of diabetes (31) and is thought to have had the largest number of individuals with diabetes in the world in 2015, with extrapolation of existing data suggesting that this will continue until at least 2030 (32). Due to the high prevalence of DM and its importance to general health, DM was evaluated as a confounding factor in the present study.

Materials and methods

Research groups. The study examined four cohorts from the Kailuan cohort study (Shown in the schematic diagram): i) Stroke cohort: According to the sex and age distribution indicated by a 1% sample of the 2005 national population ≥ 40 years of age, and considering every 2 years as an age group, personnel at the Stroke Clinical Experimental and Research Center, Capital University of Medical Sciences Affiliated Tiantan Hospital (Beijing, China) selected participants from the 101,510 individuals in the Kailuan study who participated in health examinations between January 1, 2006 and December 31, 2007 using stratified random sampling. The total number of individuals selected by sampling was 5,852, of whom 5,440 were eligible; among these, 5,219 had completed baPWV tests in the period between January 1, 2011 and December 31, 2012 and were included in the present study. ii) The aged population cohort: Retired participants in the Kailuan study with health examination results who were >60 years old between January 1, 2010 and December 31, 2011 are the alternative population. Using a cluster sampling method, the number sampled (25% of the total) was 3,064, of whom 2,464 were selected as the research cohort. iii) Pregnancy-induced hypertension cohort: From October 1976 to December 2008, 4,676 women, whose average SBP and DBP was 120.60 ± 16.82 mmHg and 71.82 ± 11.74 mmHg respectively, with single-child deliveries participated in their first health examinations in 11 hospitals of the Kailuan study between January 1, 2010 and December 31, 2015. iv) Peripheral vascular disease examination cohort: The population who received health examinations in Kailuan General Hospital and Kailuan Qianjiaying Hospital, and agreed to assessment using baPWV measurements between January 1, 2010 and December 31, 2015, of whom 14,424 were selected after baPWV detection. A total of 2464 cases enrolled in Cohort II, but only 1754 were selected based on baPWV detection and 1754 were included in the cohort II. A total of 22,681 individuals underwent baPWV detection; however, 2,096 were omitted due to the lack of BP measurements and 275 were omitted due to a history of cardio-cerebrovascular disease, leaving 20,310 participants in the current study.

Inclusion criteria and exclusion criteria. Inclusion criteria: Individuals in the Kailuan group who received health examinations in 2010, 2012 and 2014, specifically baPWV and BP measurements during 2010-2011, 2012-2013 and 2014-2015. They consented to participate in this study and signed informed consent. Exclusion criteria: i) Lack of baPWV or BP data; ii) individuals suffering from peripheral vascular diseases; iii) serious disability resulting in the inability to receive examinations; and/or iv) lack of consent to participate

in this study. The present study was conducted in accordance with The Declaration of Helsinki and was approved by the Kailuan General Hospital Ethics Committee.

Data collection. The collection of epidemiological data, anthropometric and laboratory measurements has been described in detail previously (33). The biochemical data and baPWV data were collected concurrently.

baPWV assay. baPWV was measured between 7:00 and 9:00 a.m. using a BP-203RPEIII networked arteriosclerosis test device [Omron Healthcare (China) Co., Ltd] at room temperature. Sex, age, height and weight were also recorded. Smoking was not allowed and a resting period of >5 min was required prior to measurements being recorded. Examination was performed on the left and right brachia and ankles with subjects in the supine position. The collection of epidemiological, anthropometric and laboratory data was in accordance with the 2017 ACC/AHA Hypertension Guidelines (34) for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, as were the specifications of the apparatus for measuring baPWV and BP. The distance between baPWV sampling points was calculated automatically according to the height of the subject. The path length from the suprasternal notch to the ankle (L_a) was calculated using the following formula: $L_a = 0.8129 \times \text{height (cm)} + 12.328$. The path length from the suprasternal notch to the brachium (L_b) was calculated using the following formula: $L_b = 0.2195 \times \text{height (cm)} - 2.0734$. The baPWV was calculated according to the following formula: $\text{baPWV} = (L_a - L_b) / T_{ba}$ m/sec where T_{ba} is the time interval between the front wave of the brachial waveform and the ankle waveform during simultaneous measurements of baPWV on both sides of the body. Because some studies proved the association between baPWV and the atherosclerotic vascular damage and cardiovascular risk, and we think the higher detection values is more likely to reflect the actual situation and may be helpful in the analysis of clinical outcome in the study. The highest readings were chosen as the representative values for each individual. According to the 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: baPWV <1,400 cm/sec was regarded as normal arterial stiffness and baPWV $\geq 1,400$ cm/sec as atherosclerosis and Ankle brachial index ≤ 0.9 was defined as peripheral vascular disease (34).

BP measurements. BP was measured between 7:00 and 9:00 a.m. BP was measured using calibrated mercury sphygmometers in the right brachial artery after 15 min of rest. The first and the fifth Korotkoff sounds were recorded as systolic BP (SBP) and diastolic BP (DBP), respectively (35). These two Korotkoff sounds were continuously measured three times, from which the average was calculated. Smoking was defined as having smoked >1 cigarette/day over the last 12 months, drinking was defined as having consumed 100 ml strong spirit (alcohol content >50%) daily for ≥ 1 year and physical exercise was defined as performing ≥ 3 exercise sessions/week with each lasting ≥ 30 min.

Follow-up time and definition of endpoints. The start point was defined as the time of baPWV data collection from January 1, 2010 and the last follow-up time was December 31,

2015. Cardio-cerebrovascular events were defined as an endpoint, which mainly comprised stroke (hemorrhagic and ischemic) and MI. If the events occurred more than twice in a year, the first cardio-cerebrovascular event was considered as the endpoint. The endpoints were carefully recorded by experienced professionals, and all diagnoses were confirmed by professional physicians according to medical records. Throughout the research process, all patients/subjects were either past or present employees of Kailuan Co., Ltd., and no records of patients/subjects were lost during the follow-up.

Associated definitions. Hypertension was defined as SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, with a history of hypertension or currently taking antihypertensive medication even with SBP <140 mmHg and DBP <90 mmHg (36). Normotension was defined as BP $\leq 140/90$ mmHg without a history of hypertension or antihypertensive treatment; high baPWV was defined as $\geq 1,400$ cm/sec whereas low baPWV was defined as <1,400 cm/sec. Diabetes was defined as fasting blood glucose (FBG) ≥ 7.0 mmol/l, with a history of diabetes or currently taking hypoglycemic medication even with FBG <7.0 mmol/l. (37).

Statistical analysis. The Wald test was performed as part of the Cox hazard model. All data were analyzed using SPSS 13.0 statistical software (SPSS, Inc.). Normally distributed data were presented as mean \pm standard error of the mean. Student's t-test was used for comparisons between two groups, whereas one-way ANOVA was applied for comparisons among >2 independent groups. Equal variance was compared using the least significant difference or Dunnett's T3 post hoc test. Any measured data that differed from a normal distribution were log-transformed to normal distribution, and the corresponding parameter ANOVA test was applied in the results. All counted data were presented as n (%), where the χ^2 test was used for comparisons between groups. The objects were divided into different groups according to baPWV and BP. The cumulative incidence of endpoint events was calculated using the life table method. Any differences were compared using the log-rank test, and hazard ratios (HR) and 95% CI values for the different groups of cardio-cerebrovascular events were calculated using the Cox proportional hazards model. Wald test was performed as part of the Cox hazard model. The predictive value of combined measurements of baPWV and BP, baPWV alone and BP alone on cardio-cerebrovascular events was assessed using receiver operating characteristic (ROC) curves (38). The normal approximation method was used to evaluate the area under the ROC curve (AUC). The larger the AUC, the more accurate the prediction of endpoint events. Sensitivity analysis: In order to exclude the effects of antihypertensive, hypoglycemic and lipid-lowering medication in the research, statistical analyzes were also reconducted following the exclusion of the population undergoing drug treatments. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Participant characteristics. In the study, there were 20,310 participants (13,240 male and 7,070 female) with an average age of 50.13 ± 0.09 years. According to the values of baPWV and

Table I. Participant characteristics.

Parameters	Normotension with low baPWV group (n=7,373)	Normotension with high baPWV group (n=4,651)	Hypertension with low baPWV group (n=1,674)	Hypertension with high baPWV group (n=6,612)	Total (n=20,310)	F/ χ^2 value	P-value
Age (years)	42.92±9.12	52.11±11.87 ^a	47.99±8.66 ^{a,b}	57.32±17.10 ^{a,c}	50.13±14.17	1,823.9	<0.001
Male [n (%)]	3,493 (47.4)	3,419 (73.5)	1,192 (71.2)	5,136 (77.7)	13,240 (65.2)	988.18	<0.001
baPWV (cm/sec)	1,221.21±116.47	1,625.23±247.78 ^a	1,287.59±87.61 ^{a,b}	1,807.14±358.51 ^{a,c}	1,509.95±357.20	889.82	<0.001
SBP (mmHg)	113.86±11.22	121.29±9.90 ^a	134.96±13.68 ^{a,b}	145.34±16.59 ^{a,c}	127.55±18.91	8,041.2	<0.001
DBP (mmHg)	75.53±7.15	78.66±6.37 ^a	90.55±8.47 ^{a,b}	91.21±10.58 ^{a,b}	82.59±11.01	5,946.05	<0.001
HR (bpm)	71.01±9.22	73.25±10.05 ^a	72.29±9.76 ^{a,b}	74.73±11.30 ^{a,c}	72.84±10.29	162.89	<0.001
BMI (kg/m ²)	23.97±3.68	24.52±16.77	24.53±7.32	24.18±15.94 ^a	24.20±12.35	7.36	<0.001
FBG (mmol/l)	5.13±1.03	5.55±1.59 ^a	5.56±1.65 ^a	5.92±1.87 ^{a,c}	5.52±1.56	377.71	<0.001
TC (mmol/l)	4.71±1.81	5.02±1.76 ^a	5.02±2.52 ^a	5.18±1.83 ^{a,b}	4.96±1.69	123.74	<0.001
HDL-C (mmol/l)	1.50±0.50	1.47±0.47 ^a	1.51±0.59	1.49±0.80	1.49±0.61	1.59	<0.001
LDL-C (mmol/l)	2.39±1.09	2.55±0.95 ^a	2.48±0.78 ^{a,b}	2.63±1.17 ^{a,c}	2.51±1.07	17.93	<0.001
Physical exercise [n (%)]	633 (8.4)	581 (12.5)	200 (11.9)	1,214 (18.4)	2,618 (12.9)	1.48	<0.001
Smoking habit [n (%)]	1,587 (21.5)	1,629 (35.0)	534 (31.9)	2,483 (37.8)	6,233 (30.7)	10.20	<0.001
Alcohol drinking [n (%)]	1,290 (17.5)	1,173 (25.2)	408 (24.4)	1,749 (26.5)	4,620 (22.7)	333.98	<0.001
Hypertension [n (%)]	0 (0)	0 (0)	1,674 (100)	6,612 (100)	8,286 (40.8)	578.76	<0.001
Diabetes [n (%)]	171 (2.3)	413 (8.9)	145 (8.7)	1,115 (16.9)	1,844 (9.1)	547.17	<0.001
Anti-hypertensive medication [n (%)]	0 (0)	0 (0)	583 (34.98)	3,594 (54.4)	4,177 (20.6)	55.28	<0.001
Anti-diabetic medication [n (%)]	63 (0.8)	196 (4.0)	53 (3.4)	491 (7.8)	803 (4.0)	10.96	<0.001
Anti-hyperlipidemic medication [n (%)]	37 (5.0)	70 (1.4)	30 (1.9)	208 (3.3)	345 (1.7)	8.06	<0.001

^aP<0.05 vs. normotension with low baPWV group; ^bP<0.05 vs. normotension + high baPWV group; ^cP<0.05 vs. hypertension + low baPWV group. BaPWV, brachial ankle pulse wave velocity; BP, blood pressure; SBP, systolic BP; DBP, diastolic BP; HR, heart rate; FBG, fasting blood glucose; BMI, body mass index; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table II. Cumulative incidence of cardio-cerebrovascular events in different groups.

Cardio-cerebrovascular events	Groups				Total	P-value
	Normotension + low baPWV	Normotension + high baPWV	Hypertension + low baPWV	Hypertension + high baPWV		
Myocardial infarction, [n (%)]	4 (0.1)	12 (0.3)	7 (0.4)	52 (0.8)	75 (0.4)	<0.001
Stroke [n (%)]	9 (0.1)	31 (0.7)	7 (0.4)	158 (2.4)	205 (1.0)	<0.001
Ischemic stroke	8 (0.1)	27 (0.6)	7 (0.4)	142 (2.1)	184 (0.9)	<0.001
Hemorrhagic stroke	1 (0.01)	5 (0.1)	2 (0.1)	17 (0.3)	25 (0.1)	<0.001
Total [n (%)]	13 (0.2)	43 (0.9)	14 (0.8)	208 (3.1)	278 (1.4)	<0.001

Results demonstrate a statistically significant difference in the incidence of cardio-cerebrovascular events between any two groups among all 4 research groups ($P<0.001$). baPWV, brachial-ankle pulse wave velocity. Among the 278 cases, 2 cases experienced both MI and stroke, and 4 cases experienced both ischemic stroke and hemorrhagic stroke.

BP, participants were divided into four groups: Normotension + low baPWV ($n=7,373$); normotension + high baPWV ($n=4,651$); hypertension + low baPWV ($n=1,674$); and hypertension + high baPWV ($n=6,612$). Compared with other groups, participants from the hypertension + high baPWV group exhibited significantly higher age, male ratio, baPWV, SBP, DBP, FBG, heart rate, total cholesterol, low density lipoprotein cholesterol, physical exercise, DM, and use of antihypertensive drugs, hypoglycemic drugs and lipid-lowering drugs (Table I).

Incidence of cardio-cerebrovascular events between the four groups. Within the follow-up period of 3.34 ± 1.82 years, there were 278 cases of cardio-cerebrovascular events. These included 75 cases of MI and 205 cases of stroke (two cases overlapped). Among the 205 cases of stroke, there were 184 cases of ischemic stroke and 25 cases of hemorrhagic stroke (four cases overlapped). Compared with the normotension + low baPWV group, the other three groups displayed significantly increased cumulative incidences of cardio-cerebrovascular events, MI, stroke, ischemic stroke and hemorrhagic stroke. In particular, the cumulative incidences exhibited by the hypertension + high baPWV group (3.1, 0.8, 2.4, 2.1 and 0.3% for cardio-cerebrovascular events, MI, stroke, ischemic stroke and hemorrhagic stroke, respectively), were significantly higher compared with those in the normotension + low baPWV group (0.2, 0.1, 0.1, 0.1 and 0.01%, respectively). Using the log-rank test, the cumulative incidences of the end-point events demonstrated by the different groups were revealed to be statistically significant (Table II).

Endpoint events calculation using Cox proportional hazard model. For the present study, cardio-cerebrovascular events, MI, stroke, ischemic stroke and hemorrhagic stroke were defined as dependent variables whereas the different four experimental groups were defined as independent variables, and the normotension + low baPWV group was used as a control. Cox proportional hazard model analysis was then performed after adjusting for confounding factors, including sex, age, smoking, drinking, physical exercise, TC and the use of antihypertensive medication, hypoglycemic medication or lipid-lowering medication. Compared with control group, the

HR values (95% CI) of cardio-cerebrovascular events in the normotensive + high baPWV, hypertension + low baPWV and hypertension + high baPWV groups were 4.18 (2.23-7.83), 3.00 (1.39-6.47) and 9.34 (5.14-16.96), respectively; the HR values (95% CI) of MI were 3.11 (0.98-9.87), 4.60 (1.31-16.18) and 7.14 (2.42-21.04), respectively; the HR values (95% CI) of stroke were 4.65 (2.20-9.83), 2.20 (0.81-5.99) and 10.37 (5.07-21.21), respectively; the HR values (95% CI) of ischemic stroke were 4.66 (2.10-10.34), 2.55 (0.91-7.15) and 10.83 (5.07-23.12), respectively; and the HR values (95% CI) of hemorrhagic stroke were 5.93 (0.67-52.78), 3.62 (0.31-43.03) and 6.51 (0.74-57.74), respectively (Model III; Table III). In addition, different groups were established using values from the baPWV and BP measurements. These were used as independent variables, whereas cardio-cerebrovascular events, MI, stroke, ischemic stroke and hemorrhagic stroke were defined as dependent variables. After adjusting for sex, age, smoking, drinking, physical exercise, TC, taking antihypertensive medication, hypoglycemic medication and lipid-lowering medication. The results showed that the risk of cardio-cerebrovascular events exhibited positive associations with increases in baPWV or BP (data not shown).

Predictive values of cardio-cerebrovascular events using baPWV combined with BP. ROC curves were plotted of baPWV combined with BP, baPWV alone and BP alone for the prediction of cardio-cerebrovascular events, MI, stroke, ischemic stroke and hemorrhagic stroke. For baPWV combined with BP, baPWV alone and BP alone, respectively, the AUC values were calculated to be 0.744, 0.677 and 0.698 for the prediction of cardio-cerebrovascular events (Fig. 1A); 0.726, 0.650 and 0.690, respectively, for the prediction of MI (Fig. 1B); 0.750, 0.686 and 0.700, respectively, for the prediction of stroke (Fig. 1C); 0.750, 0.684 and 0.703, respectively for prediction of ischemic stroke (Fig. 1D), and 0.722, 0.658 and 0.676, respectively for the prediction of hemorrhagic stroke (Fig. 1E). The AUC values were tested further using the normal approximation method and were calculated to be statistically significant ($P<0.05$), and the AUC of baPWV combined with BP was maximal, and it could be applied to the prediction of all 5 diseases categories.

Table III. Multivariate Cox proportional hazards model for cardio-cerebrovascular events.

Parameters	Model I ^a		Model II ^b		Model III ^c	
	Wald value	HR (95% CI)	Wald value	HR (95% CI)	Wald value	HR (95% CI)
Cardio-cerebrovascular events						
Normotension with low baPWV group	N/A	1	N/A	1	N/A	1
Normotension with high baPWV group	30.08	5.52 (2.97-10.26)	17.89	4.47 (2.39-8.35)	17.98	4.18 (2.23-7.83)
Hypertension with low baPWV group	16.17	4.12 (1.94-8.77)	10.68	3.33 (1.56-7.12)	8.92	3.00 (1.39-6.47)
Hypertension with high baPWV group	91.77	14.88 (8.50-26.07)	66.38	11.18 (6.32-19.78)	54.36	9.34 (5.14-16.96)
P-trend	N/A	<0.001	N/A	<0.001	N/A	<0.001
Myocardial infarction						
Normotension with low baPWV group	N/A	1	N/A	1	N/A	1
Normotension with high baPWV group	7.92	5.07 (1.63-15.72)	3.45	3.60 (1.15-11.26)	1.98	3.11 (0.98-9.87)
Hypertension with low baPWV group	9.88	6.89 (2.02-23.54)	6.27	4.89 (1.42-16.85)	5.02	4.60 (1.31-16.18)
Hypertension with high baPWV group	24.44	12.38 (4.48-34.25)	15.81	7.86 (2.79-22.12)	12.07	7.14 (2.42-21.04)
P-trend	N/A	<0.001	N/A	<0.001	N/A	0.002
Stroke						
Normotension with low baPWV group	N/A	1	N/A	1	N/A	1
Normotension with high baPWV group	22.07	5.70 (2.71-11.97)	14.39	4.81 (2.28-10.18)	14.1	4.65 (2.20-9.83)
Hypertension with low baPWV group	6.58	2.93 (1.09-7.87)	4.47	2.47 (0.91-6.68)	3.71	2.20 (0.81-5.99)
Hypertension with high baPWV group	67.22	16.04 (8.19-31.40)	50.06	12.76 (6.44-25.26)	41.72	10.37 (5.07-21.21)
P-trend	N/A	<0.001	N/A	<0.001	N/A	<0.001
Ischemic stroke						
Normotension with low baPWV group	N/A	1	N/A	1	N/A	1
Normotension with high baPWV group	19.18	5.58 (2.54-12.29)	12.38	4.85 (2.19-10.73)	12.23	4.66 (2.10-10.34)
Hypertension with low baPWV group	7.5	3.31 (1.20-9.12)	5.56	2.87 (1.04-7.97)	4.69	2.55 (0.91-7.15)
Hypertension with high baPWV group	60.44	16.25 (7.97-33.13)	45.77	13.37 (6.48-27.60)	38.11	10.83 (5.07-23.12)
P-trend	N/A	<0.001	N/A	<0.001	N/A	<0.001
Hemorrhagic stroke						
Normotension with low baPWV group	N/A	1	N/A	1	N/A	1
Normotension with high baPWV group	3.74	8.32 (0.97-71.24)	2.08	5.80 (0.66-51.07)	1.99	5.93 (0.67-52.78)
Hypertension with low baPWV group	2.71	7.40 (0.67-81.67)	0.52	4.95 (0.44-55.43)	0.33	3.62 (0.31-43.03)
Hypertension with high baPWV group	6.99	14.96 (1.99-112.54)	4.88	9.34 (1.19-73.59)	3.76	6.51 (0.74-57.74)
P-trend	N/A	0.045	N/A	0.155	N/A	0.347

^aModel I, cardio-cerebrovascular events, MI, stroke, ischemic stroke and hemorrhagic stroke were defined as dependent variables, the four experimental groups were defined as independent variables, normotension with low baPWV group was designated as the control group; ^bModel II, adjustment for age and sex based on Model I; ^cModel III, adjustment for smoking, drinking, physical exercise, TC, taking antihypertensive medication, hypoglycemic medication and lipid-lowering medication based on Model II. Wald values were obtained by the Wald test, which was performed as part of the Cox hazard model, and the P-trend values are P-values for a trend in HRs, which indicate that partial results have statistically significant differences in the normotension + low baPWV group vs. the other three research groups; baPWV, brachial ankle pulse wave velocity; CI, confidence interval; HR, hazard ratio; N/A, not applicable.

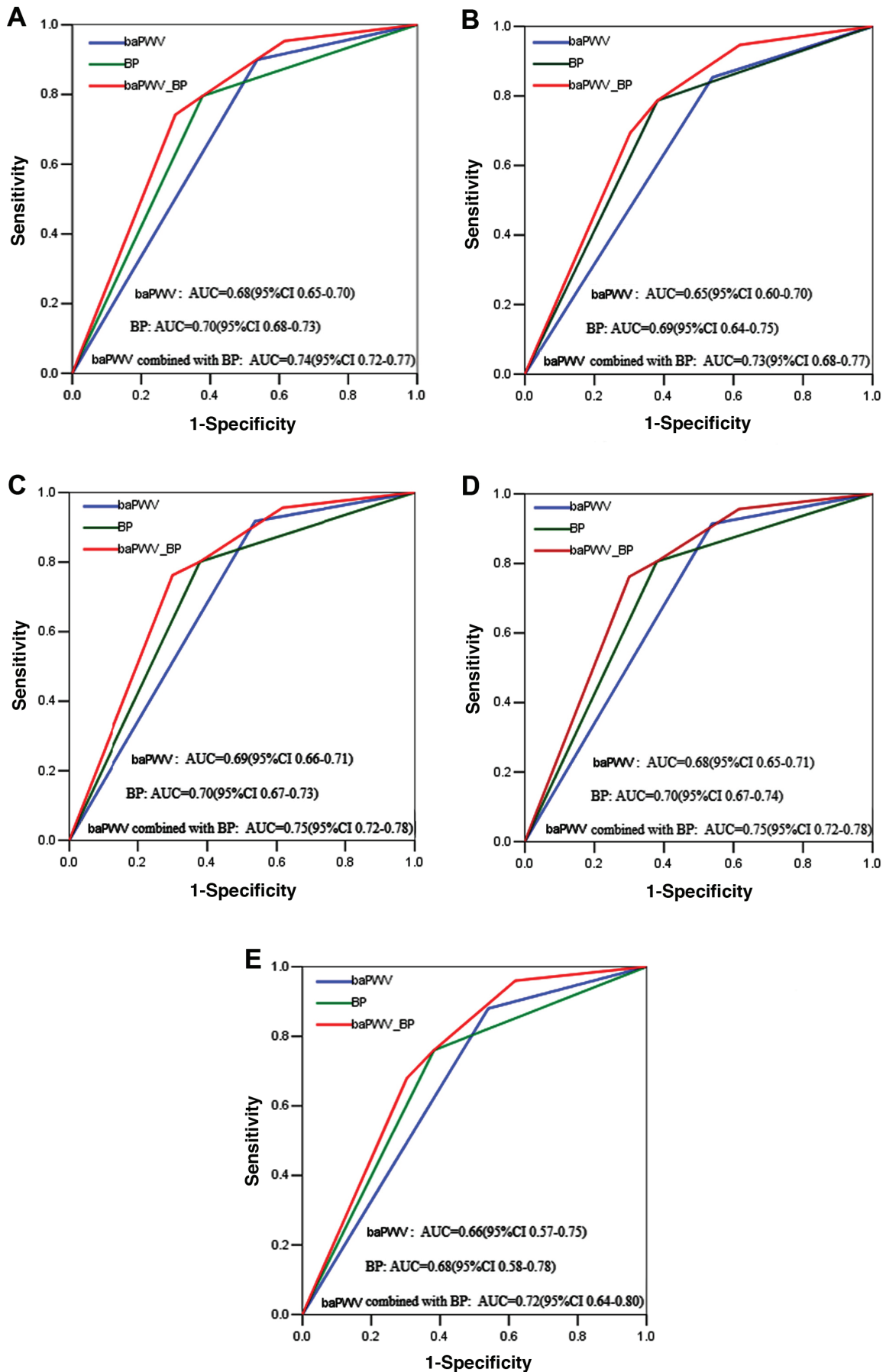


Figure 1. Receiver operating characteristic curve for predicting (A) cardio-cerebrovascular events, (B) myocardial infarction, (C) stroke, (D) ischemic stroke and (E) hemorrhagic stroke based on baPWV alone, BP alone and baPWV combined with BP. baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; AUC, area under the curve; CI, confidence interval.

Table IV. Multivariate Cox proportional hazards model for cardio-cerebrovascular events (sensitivity analysis).

Parameters	Sensitivity analysis I ^a		Sensitivity analysis II ^b		Sensitivity analysis III ^c	
	Wald value	HR (95% CI)	Wald value	HR (95% CI)	Wald value	HR (95% CI)
Cardio-cerebrovascular events						
Normotension with low baPWV group	N/A	1	N/A	1	N/A	1
Normotension with high baPWV group	14.98	3.91 (2.07-7.37)	16.55	4.91 (2.52-9.59)	15.67	4.50 (2.42-8.36)
Hypertension with low baPWV group	5.18	2.67 (1.10-6.51)	9.53	2.72 (1.65-8.39)	9.3	3.13 (1.44-6.83)
Hypertension with high baPWV group	51.08	8.48 (4.62-15.57)	54.5	10.45 (5.52-19.80)	54.92	9.89 (5.48-17.85)
P-trend	N/A	<0.001	N/A	<0.001	N/A	<0.001
Myocardial infarction						
Normotension with low baPWV group	N/A	1	N/A	1	N/A	1
Normotension with high baPWV group	1.61	2.85 (0.89-9.13)	2.01	2.60 (0.79-8.54)	1.45	3.01 (0.95-9.56)
Hypertension with low baPWV group	4.98	5.70 (1.58-20.66)	5.15	5.13 (1.46-18.01)	5.17	5.02 (1.43-17.57)
Hypertension with high baPWV group	10.41	6.04 (2.01-18.17)	11.45	6.44 (2.17-19.11)	12.2	7.37 (2.53-21.51)
P-trend	N/A	0.006	N/A	0.003	N/A	0.001
Stroke						
Normotension with low baPWV group	N/A	1	N/A	1	N/A	1
Normotension with high baPWV group	13.73	4.43 (2.08-9.44)	14.62	6.26 (2.75-14.22)	14.46	5.17 (2.48-10.82)
Hypertension with low baPWV group	0.56	1.01 (0.22-4.71)	4.06	2.75 (0.91-8.27)	3.88	2.14 (0.75-6.09)
Hypertension with high baPWV group	40.53	9.84 (4.75-20.37)	42.48	12.89 (5.84-28.48)	42.1	11.06 (5.45-22.43)
P-trend	N/A	<0.001	N/A	<0.001	N/A	<0.001
Ischemic stroke						
Normotension with low baPWV group	N/A	1	N/A	1	N/A	1
Normotension with high baPWV group	11.71	4.41 (1.98-9.86)	12.5	6.31 (2.60-15.30)	12.34	5.08 (2.32-11.14)
Hypertension with low baPWV group	0.97	1.17 (0.25-5.56)	4.97	3.24 (1.03-10.17)	4.76	2.44 (0.84-7.11)
Hypertension with high baPWV group	36.93	10.26 (4.74-22.22)	38.62	13.82 (5.88-32.45)	38.24	11.38 (5.38-24.09)
P-trend	N/A	<0.001	N/A	<0.001	N/A	<0.001
Hemorrhagic stroke						
Normotension with low baPWV group	N/A	1	N/A	1	N/A	1
Normotension with high baPWV group	1.97	5.80 (0.64-52.57)	2.29	7.77 (0.90-67.42)	2.28	7.72 (0.89-66.89)
Hypertension with low baPWV group	-	-	0.45	5.63 (0.49-64.57)	0.43	2.73 (0.17-45.05)
Hypertension with high baPWV group	3.61	7.13 (0.79-64.13)	3.84	7.83 (0.90-68.21)	3.82	8.86 (1.03-75.94)
P-trend	N/A	0.378	N/A	0.289	N/A	0.178

^aSensitivity analysis I, population receiving antihypertensive medication omitted; ^bSensitivity analysis II, population receiving hypoglycemic medication omitted; ^cSensitivity analysis III, population receiving lipid-lowering medication omitted. baPWV, brachial ankle pulse wave velocity; CI, confidence interval; HR, hazard ratio; N/A, not applicable; -, no hemorrhagic stroke.

Sensitivity analysis. Cox regression analysis was performed after the exclusion of participants currently receiving antihypertensive medication, hypoglycemic medication or lipid-lowering medication. Following the exclusion of participants receiving antihypertensive medication, compared with the normotension + low baPWV group, the HR values (95% CI) of cardio-cerebrovascular events, MI, stroke, ischemic stroke and hemorrhagic stroke were 8.48 (4.62-15.57), 6.04 (2.01-18.17), 9.84 (4.75-20.37), 10.26 (4.74-22.22) and 7.13 (0.79-64.13), respectively, for the hypertension + high baPWV group (sensitivity analysis I; Table IV). Following the exclusion of participants receiving hypoglycemic medication, the HR values (95% CI) were 10.45 (5.52-19.80), 6.44 (2.17-19.11), 12.89 (5.84-28.48), 13.82 (5.88-32.45) and 7.83 (0.90-68.21) for cardio-cerebrovascular events, MI, stroke, ischemic stroke and hemorrhagic stroke, respectively, for the hypertension + high baPWV group (sensitivity analysis II; Table IV). After omitting the participants receiving lipid-lowering medication, the HR values (95% CI) were 9.89 (5.48-17.85), 7.37 (2.53-21.51), 11.06 (5.45-22.43), 11.38 (5.38-24.09) and 8.86 (1.03-75.94) for cardio-cerebrovascular events, MI, stroke, ischemic stroke and hemorrhagic stroke, respectively, for the hypertension + high baPWV group (sensitivity analysis III; Table IV). These statistical analyses, indicate that high baPWV combined with high BP is a risk factor for cardio-cerebrovascular events.

Discussion

The results of the present study indicate that the cumulative incidences of cardio-cerebrovascular events, MI and stroke in normotensive patients with high baPWV, and hypertensive patients with low or high baPWV were higher compared with that in normotensive patients with low baPWV. The cumulative incidences of the aforementioned diseases in the hypertension + high baPWV group were markedly higher compared with those in the normotension + low baPWV group. In addition, the cumulative incidence of cardio-cerebrovascular events in the normotension + high baPWV group was higher compared with that in the hypertension + low baPWV group. Niiranen *et al* (7) observed that after a 12.6-year follow-up of 2,127 subjects, the cumulative incidence of cardiovascular events was 1.9, 8.1, 14.9 and 20.0% in normotension with low cfPWV, normotension with high cfPWV, hypertension with low cfPWV group and hypertension with high cfPWV groups, respectively.

The incidence of cardio-cerebrovascular events, MI and stroke were not only increased in the high baPWV groups. Following adjustments for confounding factors, including age and sex, the risks of the occurrence of cardio-cerebrovascular events, MI and stroke in the normotension + high baPWV, hypertension + low baPWV and hypertension + high baPWV groups were all increased compared with those in the normotension + low baPWV group. These findings showed that in the hypertension + high baPWV group compared with the normotension + low baPWV group, the occurrence risk increased 9.34-fold for cardio-cerebrovascular events, 7.14-fold for MI and 10.37-fold for stroke. However, Song *et al* (9) found that compared with baPWV in the lowest quartile with adequate hypertension control, the occurrence risk increased by only 2.57-fold with baPWV in the highest quartile with inadequate

hypertension control, which may be due to the increased focus on the population receiving antihypertension medication, leading to reduction in the risk of stroke. The present study also indicated that high baPWV maybe a risk factor for stroke, but the risk of stroke in the hypertension + low baPWV group was not markedly greater compared with that in the normotension + low baPWV group, suggesting that baPWV is a superior predictor of stroke compared with BP. The study confirmed the findings of previous studies that high baPWV and hypertension are risk factors for cardio-cerebrovascular events (39-42), and also revealed that high baPWV combined with hypertension has a superior predictive value for cardio-cerebrovascular events compared with only high baPWV alone or hypertension alone. This suggests that when evaluating the risk of cardio-cerebrovascular inpatients, baPWV should be considered as an important assessment parameter target besides BP and arterial stiffness.

When the patients currently receiving antihypertensive medication were excluded, it was found that in the hypertension + high baPWV group the risk of cardio-cerebrovascular events, MI and stroke were significantly increased compared with those in the other three groups but the HR values were reduced compared with the group treated with antihypertensive medication. This suggests that the hypertensive patients currently on antihypertensive medications are at a high-risk for cardio-cerebrovascular events. Walsh *et al* (43) found that treatment of hypertension was an important risk factor for cerebral hemorrhage. Similar patterns of results were observed among the four groups, despite the exclusion of patients taking hypoglycemic or lipid-lowering medication, suggesting that the effect of baPWV combined with BP on cardio-cerebrovascular events is independent of concomitant antihypertensive, hypoglycemic or lipid-lowering medication treatment.

High baPWV accompanied by hypertension increases the risk of cardio-cerebrovascular events caused by arteriosclerosis, suggesting that baPWV may also be an indicator of atherosclerosis. Generally, atherosclerosis is an important risk factor for hypertension, and is caused by vascular wall hardening and blood vessel lumen narrowing (44). Prolonged high BP increases the arterial hemodynamic load, leading to a decrease in arterial compliance and finally to arteriosclerosis (45,46). High baPWV causes damage to targeted organs and induces BP elevation, which reinforce each other through a feedback loop and thereby raise the risk of cardio-cerebrovascular events (7). In addition, the present study indicated that the association of baPWV with stroke exceeds that of BP, potentially due to the systemic effects of atherosclerosis. A cross-sectional study in China demonstrated that >60% stroke patients suffer from atherosclerosis (47). Cerebral infarction readily occurs in patients with atherosclerosis due to the presence of cerebral arterial stenosis, in which the affected blood vessels become vulnerable to rupture and bleeding due to stiffness and fragility.

The collection of baPWV measurements is a relatively simple procedure that can be conducted in an ordinary clinical setting, and may be combined with BP monitoring. Detecting baPWV contributes to the early detection of atherosclerosis and prediction of the occurrence of cardio-cerebrovascular events, and the observation of changes in baPWV may also help to determine the effect of antihypertensive therapy. One

of the most important aims of the antihypertensive recommendations of the European Society of Hypertension is to alleviate atherosclerosis, with reductions of baPWV and BP being equally important (48). Reducing baPWV induces improvements in vessel walls and tissues (49), which are key to successful antihypertensive treatment. Therefore, baPWV measurements have important clinical significance in the evaluation of arterial function in hypertensive patients, monitoring of treatment outcome and assessment of prognosis.

The risk factors associated with cardio-cerebrovascular events were evaluated in the present study, and an analysis of the association of baPWV with hypertension and cardio-cerebrovascular events was conducted. However, risk factors associated with cardio-cerebrovascular events potentially include many diseases and conditions. Special attention should be paid to factors not considered in this study, including controlled diabetes, dyslipidemia and body mass index (BMI). In particular, a previous study demonstrated that BMI values were significantly associated with the occurrence of cardio-cerebrovascular events ($P=0.020$) after controlling for multiple confounding factors (50). Although BMI has been found to be positively associated with BP, the correlation between BMI and BP was substantially poorer in patients taking antihypertensive medication compared with those who were untreated, demonstrating the effectiveness of treatment (51). In other studies, multiple logistic regression analysis revealed that dyslipidemia was significantly associated with age, being male, BMI, FBG and cigarette smoking, suggesting that dyslipidemia is an important risk factor for cardio-cerebrovascular events (52), and multivariable Cox's proportional hazards regression model showed that hyperlipidemia with type II DM increased the risk of cardio-cerebrovascular events (53). As mentioned above, by performing a regression analysis incorporating additional confounding factors, including underlying diseases such as controlled diabetes and dyslipidemia, sex and BMI in further research, the correlation analysis of the present study could potentially be strengthened.

Although the present study found that high baPWV combined with hypertension increased the risks of cardio-cerebrovascular events, MI and stroke, it has a number of limitations. cfPWV, which is recommended by the American Heart Association as the gold standard in the evaluation of atherosclerosis (11), was not measured and compared with baPWV in the present study. However, baPWV has been shown to correlate well with cfPWV, and a number of studies have demonstrated baPWV to be more relevant to cardiovascular risk factors compared with cfPWV (11). Ohkuma *et al* (54) suggested that baPWV has potential as a new marker of cardiovascular risk over conventional markers, it's easy to obtain and serves as an indicator of atherosclerotic vascular damage. The number of endpoint events is relatively small and the average follow-up time was 3.34 years, which was not sufficient to enable the collection of a large number of endpoint events. However, the large sample size ($n=20,310$) remedies this shortcoming to a certain degree, and it does not affect the conclusions of the present study. As many confounding factors as possible were considered when evaluating the influence of BP and baPWV on endpoint events, but other confounding factors such as environmental influences were not accounted for. Finally, the research subjects in

the present study are a Northern Chinese population, which is not representative of the global population. Therefore, the findings of the present study require further validation in other populations.

In conclusion, the findings presented in the present study suggest that high baPWV combined with hypertension increases the risk of cardio-cerebrovascular events, and the predictive value of high baPWV combined with high BP on cardio-cerebrovascular events is superior compared with either high baPWV or hypertension alone.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YW, YZ and WG conceived and designed the study. YW, YZ and JG wrote the manuscript. All data collection and statistical analysis were performed by SM, JX, ZC and SS. SW and WG reviewed and edited the manuscript. JG and SW collected and analysed clinical data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was conducted in accordance with The Declaration of Helsinki and was approved by the Kailuan General Hospital Ethics Committee. All participants signed informed consent for participation in this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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